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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Chang, Chawnshang.

Serial No. 09/711,585

Confirmation No. 7198

Filed: November 13, 2000

For: MUTUAL SUPPRESSION BETWEEN SEX HORMONE RECEPTORS AND OTHER NUCLEAR RECEPTORS

Group Art Unit: 1646

Examiner: Basi, Nirmal Singh

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M.G.J
5/6/02

PRELIMINARY AMENDMENT

U. S. Patent and Trademark Office
BOX SEQUENCE
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April 24, 2002

Sir:

This is responsive to the March 26, 2002 Office Communication, Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures issued regarding the above-identified patent application. A copy of this document is enclosed. Also included is an Appendix A containing the marked-up specification section.

Amendment

Please amend the specification as follows.

Please replace paragraph 0051 with the following paragraph.

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[0051] Two potential impacts of these new findings are significant. First, the role of AR in the modulation of androgen target genes may be expanded. In addition to activation of classic

androgen target genes containing androgen response elements (GGA/TACAnnnTGTTCT) (SEQ ID NO:8), AR may also signal through heterodimerization with TR4, resulting in the repression of various TR4 target genes, which contain a consensus response element (AGGTCA) in a DR orientation ($AGGTCA(n)_xAGGTCA$, x = 0-6) (SEQ ID NOs: 1-7). Data from our gel shift assays showed that the binding preference of TR4 for the natural TR4RE identified in various target genes, was in the order of DRI (CRBII-TR4RE) > DR2 (SV40-TR4RE) > DR4 (TRE-TR4RE) > DR5 (RAREβ-TR4RE) > DR3 (VDRE-TR4RE), with the IC_{50} varying widely from 0.023 ng to 2.0 ng. Lee, et al., *J: Biol. Chem.* 273, 13437-13443 (1998); Lee, et al., J: *Biol. Chem.* 272, 12215-12220 (1997); Lee et al., *J Biol. Chem.* 274, 16198-16205 (1999); Lee et al. ,*J Biol. Chem.* 270, 30129-30133 (1995). Among these TR4 target genes that could be suppressed by AR, HBV suppression might be especially interesting as it provides the first evidence that AR may play a suppressive role in the HBV expression. Whether this may contribute to the male-preference Hepatitis B or hepatoma will be an interesting topic for future study. Secondly, we have demonstrated that the classic androgen-signaling pathway (AARARE) can be influenced by TR4. This not only represents the first mechanism to distinguish between receptors (AR, GR, and PR) that share the same hormone response elements (found in MMTV or other target genes), but also provides a new potential target through which to block the androgen action. The long-term impact of these two new events may be in providing us another approach in the design of the new generation of drugs with androgenic or antiandrogenic activity with which to treat androgen-related diseases.

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Remarks

Enclosed herewith is a diskette containing the Sequence Listing for this application in computer readable form (CRF) and a paper copy of the Sequence Listing in compliance with 37 C.F.R. §§ 1.821-1.825. Applicant hereby certifies that the information in both the computer readable form and the paper copy of the Sequence Listing is the same and includes no new matter.